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Please address correspondence to:
The Commissioner
New Zealand
Patent Office,
Private Bag, Lower Hutt. N.Z.

In reply, please quote

1 September 1987

A.J. Park & Son
WELLINGTON

Dear Sirs

Patent Application No.212766
THE WELLCOME FOUNDATION LTD &
THE GENERAL HOSPITAL CORPORATION
Your ref: P130215 THS

The matters raised in this letter should be dealt with as promptly as possible. The time prescribed by s.19 of the Patents Act 1953 for complying with all the requirements in connection with this application has been extended under the provisions of s.93(1) to 14 DEC 1988.

The Examiner, Mr Dunbar, reports:

A. As a result of investigation under s.13 it appears that the invention, at least so far as it is claimed in claims 27 and 28, has been published in the following British patent applications:

2002758A, available for inspection at the Patent Office Library since 29 June 1979;

2061929A available since 24 August 1981. It also seems that some of these compounds at least are known from J. Chem Soc. Perkin Trans I, 2067 of 1982. See pages 13 and 14. This publication has been available at the Library Centre DSIR since 12 JUN 1984.

The Commissioner may refuse to accept the complete specification unless the applicant either;

(a) shows that the priority date of his claim is not later than the date on which the cited document was published in New Zealand, or,

212766 (Continued):

(b) satisfactorily amends the complete specification.

B. The following matters need attention in order to comply with s.10(4):

1. Claim 3, line 2 and claim 20, line 2: "is" should read "are" here.

2. Claim 17, lines 2/3: these lines should apparently read "administering to a mammal a muscle relaxation amount...".

3. Claims 27 and 28 do not appear fairly based on the disclosure. The only specific compounds of formula (2) disclosed are those wherein symbol Y represents hydroxy and the method given for the preparation of compounds of formula (2) enables only those wherein Y represents hydroxy to be obtained. See page 10. Some restriction of compounds claimed is necessary accordingly.

C. Claim 17 does not relate to an invention within the meaning of s.2 in that it concerns medical treatment of humans. Amendment is necessary in this respect. S.12(2).

D. Page 9, lines 9 and 11 under formula (3): it seems that "formula (3)" rather than "formula (2)" should be referred to here. S.10(3)(a).

E. Patents Form 43's filed on 30 Jul 1985 and 10 Jan 1986 are acknowledged. The amendments proposed may be made.

F. The title on page 1 does not sufficiently describe the invention as required by s.10(1). A suggestion is "Isoquinoline Derivatives".

G. Pages 24-30 are not sufficiently clear and fresh pages, in duplicate, are requested under Regulation 10(b).

Yours faithfully

H. BURTON
Asst Commissioner of Patents

Per: D. I. Dunbar

7. A compound according to claim 6, wherein the RS-RS and the RR-RS diastereoisomers together constitute greater than 90% (w/w) of the mixture.

8. A compound according to claim 5, wherein the mixture comprises from 1 to 15% (w/w) of the RR-RR diastereoisomer, from 38 to 50% (w/w) of the RR-RS diastereoisomer, and from 40 to 56% (w/w) of the RS-RS diastereoisomer.

9. A compound of claim 1 wherein the central double bond is in the (E) configuration or (Z) configuration.

10. A compound of claim 9 which is the RS-RS diastereomer.

11. A compound of claim 9 which is the RS-RR diastereomer.

12. A mixture comprising the RS-RS, RS-RR (trans-cis) and RR-RR diastereomers of a compound of the formula (1) as described in claim 9.

13. A compound or mixture of any one of claims 1 to 12 in which X is a pharmaceutically acceptable anion.

14. A compound or mixture of any one of claims 1 to 12 in which X is chloro.

wherein X^- is as defined in claim 1 and Y can be hydroxy, chloro, bromo, iodo, or tosyloxy, with a compound of formula (3):

$$ZOCCH_2CH_2CH=CHCH_2CH_2COZ \qquad (3)$$

wherein Z is hydroxy, chloro, bromo or C_{1-4} alkylcarbonyloxy.

19. The process of claim 18 in which the configuration of the compound 1 at both the C(1) and the C(1') carbon atoms is the R configuration.

20. The process of claim 19, wherein the groups attached to the alkenic double bond configuration is in the E configuration.

21. The process of claim 20, wherein the compound is the RS-RS or RR-RS diastereoisomer.

22. The process of claim 18, wherein the central double bond of the compound 1 is in the (E) configuration or (Z) configuration.

23. The process of claim 22 which is the RS-RS diastereomer.

24. The process of claim 22 which is the RS-RR diastereomer.

25. The process according to any one of claims 18 to 24, wherein X is chloro.

26. The process according to claim 18 wherein the compound 1 is selected from:

(E)-(1R,2R)-2-[3-[(7-Carboxyheptanoyl)oxy]propyl]-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium chloride,

(E)-(1R,2S)-2-[3[(7-Carboxyheptanoyl)oxy]propyl]-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium chloride,

cis-1,2,3,4-Tetrahydro-2-(3-hydroxypropyl)-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl) isoquinolinium chloride,

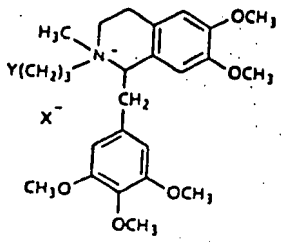
trans-1,2,3,4-Tetrahydro-2-(3-hydroxypropyl)-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl) isoquinolinium chloride,

2,2'[(E)-4-Octenedioylbis(oxytrimethylene)]bis[1R,2R-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] dichloride.

(E)-(1R,1'R,2R,2'S)-2,2'-[4-Octenedioylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7-dimethyoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] dichloride,

2,2'-[(E)-4-Octenedioylbis(oxytrimethylene)]bis[(1R,2S)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] dichloride.

27. A compound of formula (2):



(2)

wherein X is an anion and Y is hydroxy, chloro, bromo, iodo or tosyloxy.

28. A compound of claim 27 in which X is chloro.

29. A compound of formula 1 as defined in any one of claims 1 to 15 for use in human or veterinary medicine.

30. A compound of formula 1 as defined in any one of claims 1 to 15 for use as a muscle relaxant.

31. Use of a compound of formula 1 as defined in any one of claims 1 to 15 in the manufacture of a medicant for muscle relaxation.